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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,529	08/04/1999	SUSAN MARY KINGSMAN	9192.9USWO	7151

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/254,529	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-34,36-38 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26-34, 36-38, 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 04/15/04 has been acknowledged.
Claims 24, 26-34, 36-38 and 40-43 are pending.

The finality of the rejection of the last Office action is withdrawn in view of new ground of rejections below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 26, 28-30, 33-34, 36-38 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lisziewicz (WO92/21750, 1992, ref of record), Hope et al (PNAS, 87:7787-7791, 1990, ref of record) and Riviere et al (US 6544771, 2003)

The scope of the instant claims encompasses a retroviral vector or a DNA construct encoding a packageable RNA genome for a retroviral vector particle, wherein the retroviral vector particle, when in the form of a DNA provirus, comprises: (i) a 5'LTR comprising an HIV U3 and R region having Tat inducible promoter activity (ii) at least one retroviral polynucleotide response element (PRE) which is responsive to a nucleus to cytoplasm transport factor, wherein the PRE is a retroviral Rev response element (RRE); wherein the PRE is located within an intron in a transcription unit of the provirus, wherein the intron is flanked by a retroviral splice donor (SD) site and a retroviral splice

acceptor (SA) site derived from different retroviruses, wherein the construct comprises an insertion site within the intron containing the PRE at which one or more nucleotide sequences (NS) may be inserted; and wherein the construct is operably linked to a promoter.

Regarding claims 24, 26-30, 33-34, 36-38 and 40-41 Liziewicz teaches a retroviral vector (MLV) incorporating HIV Rev/RRE system, wherein the RRE is located within the transcriptional unit of the foreign gene or within the transcriptional unit of the vector (page 6, line 21-32 page 9, line 1-4 and fig. 1-4). Liziewicz further teaches that the vector contain an internal promoters operably linked to the foreign gene and DNA sequence encoding the RRE (page 9, line 5-26). The cited art teaches that RRE can be inserted in the vector in the LTR, in front of the foreign gene, behind the foreign gene or within an intron of the foreign gene (page 9, line 5-11). Regarding claim 24(i), 34(i), and 37(i) The cited art teaches that the preferred LTRs include the MLV LTRs or HIV LTRs (page 8, line 5). The retroviral vector (MLV) as taught by Liziewicz include a strong promoter (HIV LTR) which is switched on in the presence of the virus or viral-transactivator protein (**tat**), but in the absence of viral infection does not express the encoded gene product (page 12, line 14-25 and fig-4, page 13, line 19-24). Therefore, Liziewicz clearly teaches a retroviral vector wherein the nucleotide sequence of interest is located within an intron in the transcription unit of a provirus and the gene expression is only limited to HIV infected cells in the presence of tat.

Regarding claims 24, 34 and 37 Hope et al teaches that HIV-1 transactivator Rev is a nuclear protein that regulates the expression of HIV transcripts by binding to the Rev response elements (RRE) present in the HIV transcripts. Hope et al further teaches a retroviral vector comprising splice donor sequence, RRE and splice acceptor sequences, wherein the gene of interest (CAT) is located within the splice donor and splice acceptor sites (page 7787, abstract; page 7788, fig-1). Furthermore, the transcripts produced by this vector harbor a single intron, which contain CAT coding sequences (page 778, col.1. Para.1). Regarding claims 40-41 the cited art further teaches the infection of MT4 cells with recombinant viral particles in vitro (page 21 col.2 para.2).

Even though the combined teaching of Liziewicz and Hope suggest a tat/rev responsive retroviral vector the cited does not teach splice donor (SD) and splice acceptor (SA) sites derived from different retroviral vectors that flanks the provirus intron and gene of interest.

Regarding claims 24, 34, 37 and 42-43 Riviere teaches a recombinant retroviral vector containing splice donor and splice acceptor cites obtained from different retroviruses. The cited art teaches a recombinant retroviral vector useful to transfect cells, comprising: (i) a 5' LTR derived from a retrovirus of interest; (ii) a splice donor site located 3' to said 5' LTR; (iii) a Psi packaging site located 3' to said splice donor site; (iv) a consensus splice acceptor site, located 3' to said Psi packaging site; (v) an insertion site for a gene of interest located 3' to said consensus splice acceptor site; and (vi) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site (Col. 28, lines 44-57; Col. 29, lines 15-30, Col. 30 lines 50-65). Given the broadest reasonable interpretation the cited art clearly anticipate a retroviral vector comprising splice donor and splice acceptor sites derived from different retroviruses.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the retroviral vector (MLV) as taught by Liziewicz, by incorporating a nucleotides of interest within the splice acceptor site (HIV) as taught by Hope et al. One would have been motivated to do so because the insertion of a RRE (HIV) into the intron of foreign gene and within splice donor and splice acceptor sites provides the regulation of the expression of a foreign gene by RRE element which is only switched on in the presence REV protein. It would have been further obvious to modify the combined teaching of Liziewicz and Hope by substituting splice donor and splice acceptor sites derived from different retroviruses. One would have been motivated to incorporate HIV splice acceptor site to conserve the functionally of HIV RRE in the construct. One would have a reasonable expectation of success because the regulation of HIV LTR by Tat-protein and RRE by Rev-protein has been a well characterize phenomenon in the art at the time the instant invention was made. In addition making a retroviral vector containing splice donor and splice acceptor sites derived from different retroviruses is well within the reach of one ordinary skill in the art, since art at the time of

filing clearly teaches that even consensus sequence comprising a splice donor and splice acceptor sites are capable of producing spliced transcripts. Thus the invention as claimed is prima facie obvious in view of the prior art of record.

Claim Rejections - 35 USC § 112

Claim 37 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the office action mailed on 12/17/03.

Response to arguments

The applicant argues that the instant claim does not require Rev-dependency. The applicant argues that the claim requires at least one retroviral polynucleotide response element (PRE), which is responsive to a nucleus-to-cytoplasm transport factor. The applicant argues that the functional equivalents to the lentiviral Rev/RRE systems can be used in the instant invention in view of specification on page 7. The applicant argues that applicants were in possession of the claimed genus of retroviral polynucleotide response element (PRE), because numerous representative of the genus are described in the specification and were known prior to the time of the invention.

However, this is found NOT persuasive because the scope of invention as claimed encompasses: any retroviral polynucleotide response element (PRE), which are responsive to any nucleus to cytoplasm transport factor. At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity. Furthermore the specification only disclosed a HIV Rev response element, which is responsive to HIV Rev. Besides HIV Rev response element, which is

responsive to HIV Rev protein the specification fails to disclose any other functional equivalent of Rev response element and functional equivalent of HIV Rev protein. In addition, it is unclear what is included or excluded in a retroviral particle that comprises all or a portion of any oncoretroviral genome. Limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only disclosed HIV Rev response element (RRE), which is responsive to HIV Rev protein but fails to disclose any other PRE that is responsive to a nucleus to cytoplasm transport factor.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case the variants (as claimed) has been defined only by a statement of function that broadly encompasses an element that is responsive to any and all nucleus to cytoplasm transport factors, which conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a

description of only one member of this genus is not representative of the variants of genus and is insufficient to support the invention as claimed.

Claim 37 stand is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct which when in the form of DNA provirus comprises HIV 5'LTR that comprises HIV U3 and R regions having HIV Tat inducible activity and comprises HIV RRE responsive to HIV Rev (PRE), does not reasonably provide enablement for a DNA construct which when in the form of a DNA provirus comprises any polynucleotide response element (PRE) that is responsive to any nucleus to cytoplasm transport factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 12/17/03.

Response to arguments

The applicant argues that undue experimentation is not required in the instant case. The quantity of experimentation required to substitute Rev/RRE equivalents of HIV Rev/RRE is low. The applicant further argues that one skill in the art would be able to use the instant specification and knowledge available in the art at the time of filing to make a retroviral particle comprising any known Rev/RRE system.

However, this is found NOT persuasive because invention as claimed requires an undue amount of experimentation, since the specification as filed only teaches making a HIV based retroviral particle. The scope of invention as claimed encompasses any retroviral polynucleotide response elements (PRE), which are responsive to any and all nucleus to cytoplasm transport factor.

At best the specification as filed disclosed a retroviral particle and DNA construct which when in the form of DNA provirus comprising a HIV Rev response element (a PRE or a retroviral response element), which is responsive to HIV Rev (a nucleus to cytoplasm transport factor). Besides HIV Rev response element, which is responsive to HIV Rev protein the specification fails to disclose any functional equivalent of Rev response element and functional equivalent of HIV Rev protein.

State Of Art And Predictability:

The state of the art at the time of filing teaches that the Rev response element (RRE) is a 244-nt region in the env gene of HIV-1 that mediates transport of viral mRNA from the nucleus to the cytoplasm. Initially, the Rev protein binds with high affinity and specificity to a highly structured 30-residue region of the stem-loop IIB domain often termed the Rev binding element (RBE). See Huang et al PNAS USA. 97(10): 5107-5112, 2000, page 5107 col.1 (ref. of record). In type D retroviruses, such as the simian retrovirus type 1 (SRV-1), genomic RNA is exported by cellular factor(s) that interact with a conserved cis-acting RNA element, the constitutive transport element (CTE) which is distinct from the REV-RRE system (Saavdra et al. Curr Biol. 7(9):619-28, 1997 page 619, see Conclusion, ref or record). Besides REV-RRE system the applicant fails to disclose any polynucleotides response element or retroviral response element that is responsive to a nucleus to cytoplasm transport factor. Given the applicant's disclosure it is unclear how one skill in the art would identify and use a functional equivalent of HIV Rev that would bind to a functional equivalent of Rev response element. The invention as claimed encompasses structural and/or functional variations in both RRE and Rev components, wherein function of one is defined as function of other. In addition it is unclear how one skill in the art would use the retroviral particles and DNA construct (as claimed) to transduce any target cell, since the applicant fails to disclose the claimed structural variants required to make the DNA construct and/or retroviral particles. Therefore, considering the state of the art at the time of filing the applicant has not presented enablement commensurate in scope with the claims.

Considering the state of the art at the time of filing making any and all Tat inducible promoters, variants of RRE or Rev that have REV/RRE-like functional activity is not considered routine in the art and without sufficient guidance to a specific variants (as claimed) the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore,

one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER